REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing claim amendments and the following commentary.

I. Status of the Claims

Claims 1-27, 37-38, 41, 44-50 and 61-63 were previously cancelled. Claim 28 has been amended with exemplary support in the specification, e.g., at page 10, lines 14-15, 25, 29 and 35. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 28-36, 39-40, 42-43, 51-60 and 64-72 will be pending.

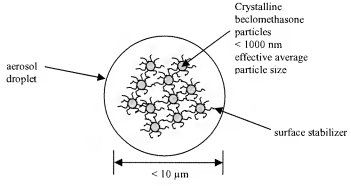
II. Rejection of Claims under 35 U.S.C. §103(a)

Claims 28-36, 39-40, 42-43, 51-60 and 64-72 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over BECOTIDE® in view of U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge") and U.S. Patent No. 5,525,623 to Spear et al. ("Spear"), as evidenced by U.S. Patent No. 5,049,389 to Radhakrishnan ("Radhakrishnan") and "Glaxo History." Applicants respectfully traverse the rejection.

At the outset, Applicants note that the primary reference, BECOTIDE®, was not made of record in any of the PTO-892 forms and no copy of the primary reference was provided by the PTO. Applicants further note that the Examiner relies on Radhakrishnan and Glaxo History to "evidence" the alleged properties of BECOTIDE®. As a copy of BECOTIDE® is unavailable, Applicants cannot directly respond to the teachings of the primary reference. Should the Examiner maintain BECOTIDE® as the primary reference, Applicants respectfully request that BECOTIDE® be properly made of record and that a copy be provided.

A. A drug suspension is distinguishable from a drug dispersion.

The claimed invention is directed to a method of treating a respiratory illness using an aerosol composition, which comprises droplets having a particle size of less than 10 microns. The aqueous droplets comprises, *inter alia,* crystalline beclomethasone particles having an effective average particle size of less than 1000 nm. In other words, the claimed invention has two defined-sizes: one is for the aerosol droplets, which have a size of less than 10 microns; and the other is for the crystalline beclomethasone particles, which have an effective average particle size of less than 1000 nm. The aerosol composition of the claimed invention is depicted in the diagram below:



The Examiner explicitly acknowledges that "BECOTIDE® is silent as to the particle size and crystalline nature of the suspended beclomethasone dipropionate particles" (Office Action, page 6, lines 13-14). This is because BECOTIDE® is "an aqueous ***suspension*** of beclomethasone dispropionate" as the Examiner admits (*Id*, page 4, line 15) such that no solid crystalline particles are in existence.

In contrast, the claimed invention requires that the therapeutic agent, e.g., beclomethasone, be dispersed "in a liquid medium in which it is essentially insoluble" to form a ***dispersion*** (specification, page 10, lines 14-15, 25, 29 and 35).

As one skilled in the art would have understood, there is a defined and well-established distinction between a drug suspension and a drug dispersion. Drug suspensions and dispersions

are not fungible or equivalent to one another because there are well-established structural and chemical distinctions between the two that are recognized by skilled artisans who practice in the field of drug formulation.

In the context of drug formulation, a ***suspension*** is a one-phase continuous medium that contains particles (~1-1000 nm). The American Heritage Dictionary defines a suspension as:

> A system in which microscopically visible particles are dispersed throughout a less dense liquid or gas from which they ***are easily filtered*** but not easily settled because of system viscosity or molecular interactions.

A ***dispersion***, however, is a two-phase system in which one phase consists of finely divided particles which are distributed throughout an external phase that prevents those particles from settling or being filtered, such as a colloid. The American Heritage Dictionary defines a colloid as:

> A system in which finely divided particles, which are approximately 10 to 10,000 angstroms in size, are dispersed within a continuous medium in a manner that ***prevents them from being filtered easily*** or settled rapidly.

As such, Radhakrishnan fails to teach an effective particle size of the beclomethasone crystalline particles as recited in claim 28 because beclomethasone is in a dissolved state in the aqueous suspension. Rather, the particle size distribution illustrated in Figure 4 and discussed at column 16, line 53 through column 17, line 17 is "the aerosol particle size," i.e., the size of the droplet. *See* Radhakrishnan, column 32, lines 34-36 ("A graphic plot of this data by standard methods gives the mass median aerodynamic diameter (MMAD) of the aerosol droplets (FIG. 4, 5).")

B. A reason of combining the references is lacking.

In an attempt to remedy the acknowledged deficiencies of the primary reference, the Examiner cites Liversidge for the alleged teaching of crystalline active agent particles having an effective average particle size of less than 1000 nm.

As discussed *supra*, BECOTIDE® is an aqueous ***suspension*** of beclomethasone, which does not have any solid, crystalline beclomethasone particles present. Liversidge describes "***[d]ispersible particles*** consisting essentially of a crystalline drug substance…[having] an effective average particle size of less than about 400 nm" (abstract, emphasis added).

Pursuant to MPEP 2143.01, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)."

In the present case, one skilled in the art would not have any reason to combine the teaching of the primary reference with that of Liversidge because it is impossible to apply Liversidge's method of reducing particle size to the primary reference as there is no crystalline particles existing in BECOTIDE®. Accordingly, the Examiner fails to establish a *prima facie* case of obviousness.

Spear is cited for the alleged teaching of a jet nebulizer or an ultrasonic nebulizer for creating aerosols (Office Action, page 6, lines 9-10), but fails to compensate for the deficiencies of the primary and the secondary references as discussed above. Therefore, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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